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Medical Progress

Australia Antigen and the Revolution In Hepatology

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AUSTRALIA ANTIGEN OR HEPATITIS associated antigen (HAA) was first detected in the serum of an Australian aborigine by using as an antiserum a precipitating antibody which developed in hemophilia patients who had received multiple transfusions.[1,2] Since that time it has been shown that this antigen is a particle intimately associated with, or a causative agent of, viral hepatitis.[3,4] The steps leading to this determination represent a fascinating saga of medical and historical serendipity.

In 1963 Dr. B. S. Blumberg and his colleagues were in the midst of a systematic study exploring inherited variations in serum proteins. This was part of an extensive study of inherited and acquired antigens to which hemophilia patients may have developed antibodies following repeated transfusions.[1] During these studies an unusual antibody was found in the serum of a patient with hemophilia who had received many transfusions. In the initial experiments the antibody was found to react with the serum of an Australian aborigine but not with other sera in the panel. It was therefore called Australia Antigen (abbreviated Au(1)). The antigen was present in only 0.1 percent of the general United States population,[5] but was detected in the blood of 8 of 70 patients with leukemia.[3,6] Subsequently HAA was found in 28 percent of 310 patients with Down's syndrome who were in institutions but was rarely present among patients with Down's syndrome living out of institutions.[3,7] Equally confusing was the finding of HAA in 5 percent of apparently normal people living in several Asian and oceanic countries. This led to studies which suggested Mendelian inheritance.[8,9] The antigen was also found in seven of 38 patients with acute granulocytic leukemia and four of 30 patients with chronic lymphocytic leukemia. Many of these patients were subsequently found to have received transfusions and to have liver disease.[3]

Further studies revealed the antigen to be associated with long incubation period or post-transfusion hepatitis. Initial studies showed HAA to be detected in up to 58 percent of such patients, as determined by immunodiffusion studies.[3,10] The association of HAA with acute hepatitis was quickly confirmed by Okochi and Murakami.[6] Early studies were done primarily using the relatively insensitive Ouchterlony immunodiffusion technique. However, in 1969 two groups independently described highly sensitive complement fixation assays for HAA.[11,12] This led to studies revealing that by testing serial sera, HAA could be detected in up to 98 percent of 130 patients with post-transfusion hepatitis.[11] These studies firmly established the association of HAA with acute hepatitis.

After partial purification by sucrose density gradient ultracentrifugation, HAA was examined under the electronmicroscope by Bayer.[13] HAA was found to be composed of 200-Angstrom

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particles with sub-units 30 Angstroms in diameter. Immunofluorescent studies consistently demonstrated HAA in and around the nuclei of liver cells of patients with viral hepatitis and HAA in their blood.[14] The antigen was not demonstrable in other forms of acute liver disease, either by immunofluorescence studies of liver preparations or by evaluation of the blood of patients, using immunodiffusion techniques. Prince, using a similar method, demonstrated the presence of an antigen in the sera of patients with post-transfusion hepatitis but not in the sera of patients with infectious hepatitis. He designated this antigen as "SH" antigen.[15] Subsequent studies have shown that SH antigen forms a band of identity with HAA.[16] Accordingly, hepatitis associated antigen or HAA, Australia antigen or Au(1) and SH antigen, are now thought to be identical determinants. Because of the association of Australia Antigen with acute hepatitis, evidence that it can be transmitted by transfusion, together with the electronmicroscopic appearance and its demonstration by immunofluorescence studies in or on the nuclei of liver cells, it has been suggested that HAA may indeed by a virus which could be an etiologic agent of hepatitis.[10]

In 1969 Wright and his colleagues[17] and my colleagues and I[18] independently demonstrated the presence of HAA in the sera of patients with chronic active liver disease. These studies demonstrated that the antigen may persist for weeks, months or years among patients with chronic liver disease even though the liver is cirrhotic. Blumberg and his colleagues had already demonstrated the presence of the antigen among patients with Down's syndrome and anicteric chronic liver disease.[3] It has accordingly been suggested that HAA may be acting as a "slow" virus. London and his colleagues suggested that these findings, together with the appearance of HAA among patients with Down's syndrome, leukemia and lepromatous leprosy, may indicate an association with some form of immunologic deficiency.[19]

Recently Australia antigen subtypes have been defined[20,21,22] and the possible clinical implications of such subtypes have been explored. In addition to the initial association of HAA with acute hepatitis and the subsequent demonstration of HAA in chronic active hepatitis and postnecrotic cirrhosis, further studies have demonstrated the variable presence of HAA among patients with primary biliary cirrhosis, neonatal hepatitis,[23,24,25,26] hepatoma,[27] and periarteritis nodosum.[28,29] Finally, circulating antigen-antibody complexes have been demonstrated among patients whose HAA complement fixation tests were anti-complimentary. Accordingly, therapeutic and prognostic significance has been attached to the presence of an anti-complimentary or "AC" HAA assay.[30]

Assay Systems

Several valuable tests are now available for the detection of HAA. When antigen is present in high concentrations most of the available assay systems are capable of detecting it. However, antigen that is present in low concentrations may be detected only in the more sensitive systems. The Ouchterlony agar gel diffusion system was the first assay developed for the detection of HAA.[31] This system usually requires at least 24 hours before results are available. Current data suggest that this is the least sensitive assay for the detection of HAA.[32] Counter-electrophoresis is one of the most widely used assay systems for screening for HAA. This system offers the advantages of being rapid, relatively inexpensive and easy to perform, and it is more sensitive than standard immunodiffusion systems. However, this assay system lacks the sensitivity of the following tests. Complement fixation is a highly sensitive means of detecting HAA.[11,12] The standard test requires 24 hours. Variations of the test may be performed within three hours. This assay is relatively inexpensive and is sensitive, but requires a skilled technician and a reliable control system. Recently an automated complement fixation assay was described.[32] This system, which requires only 45 minutes for the performance of 60 tests on a single channel of an autoanalyser, may provide a rapid automated inexpensive means of screening in large blood centers. The hemagglutination inhibition assay is thought to be a very sensitive, relatively rapid and inexpensive test for the detection of HAA.[33] This is a new test and has not been thoroughly evaluated. Initial data suggest that this may be a sensitive and reliable assay system which will yield results within a short period and can easily be performed. The reagents for this system currently are relatively expensive. This assay system may lend itself to automated procedures.

The most sensitive assay for HAA is the radioimmunoassay.[34] This assay takes several days to perform, is technically difficult and requires highly trained personnel for performance and interpretation. Currently this assay system does not lend itself to rapid, large-scale screening procedures.

Physical and Chemical Properties

Electronmicroscopic studies of partially purified antigen preparations have revealed virus-like particles 200 Angstroms in diameter.[13] These particles may be tubular or spherical in shape and may contain a dense core. Most particles appear empty. The surface consists of symmetrical polyhedral sub-units 30 Angstroms in diameter. These particles may be agglutinated by specific antibodies. Other studies have revealed the occasional presence of large oval particles 200 mμ in diameter. Recently studies have demonstrated small amounts of RNA in purified antigen preparations. The characteristics previously described are entirely consistent with those of a small virus. However, Koch's postulates have not been fulfilled. Krugman has recently shown that the infectious moiety of HAA may be inactivated by heat, and in this manner he has produced an experimental hepatitis vaccine.[31]

Acute Hepatitis

Studies by several groups, including the important contributions of Blumberg,[3] Prince,[15] Giles,[35] and Krugman,[36,37] have established a definite association between HAA and long incubation period or serum hepatitis. In one series HAA was detected in 97 percent of 40 cases of post-transfusion hepatitis but was not detected in 41 consecutive cases of short incubation period or infectious hepatitis.[37] With the development of the HAA complement fixation assay, Shulman was able to demonstrate that HAA could be detected in at least one of four serial sera of 98 percent of patients with documented post-transfusion hepatitis.[11] Some investigators have associated the antigen with short incubation period hepatitis or infectious hepatitis. These findings have not been uniformly observed. It has been suggested that the infrequent association of HAA with infectious hepatitis may reflect the fecal-oral transmission of HAA hepatitis. Among the many important contributions made by Krugman to our understanding of hepatitis was the demonstration that the agent of long incubation period hepatitis, though usually transmitted through blood products, could also be transmitted by the oral route.[36] The test for HAA is a helpful aid in differentiating between infectious and serum hepatitis, or between serum and drug-induced hepatitis. A negative HAA test does not rule out the presence of long incubation period hepatitis because the duration of antigenemia may be transient. The antigen may be present for as short a period as two or three days, or as long a period as 21 days. It may not be detectable shortly after the onset of jaundice and it may rapidly disappear after the transaminase has reached its peak.

During past years it has been reported that in the United States the annual rate of post-transfusion hepatitis amounts to approximately 30,000 cases. Furthermore, it has been estimated that there may be up to 3,000 deaths a year as a direct result of post-transfusion hepatitis.[38] Most blood banking centers have now instituted routine testing of blood and blood products for HAA. In some centers the frequency of post-transfusion hepatitis has been reduced by 25 percent or more, but nowhere has it been eliminated. A number of techniques are available for HAA testing. It is unfortunate that those which lend themselves most easily to large scale screening procedures are the least sensitive assays. The more sensitive assays, such as the radioimmunoassay, the hemagglutination inhibition test and the complement fixation assay, require time, money and technical skill. The application of automated procedures to these assay systems may provide rapid, inexpensive and highly sensitive assays through routine use in large blood banks.[32]

Initial studies reported by Krugman have suggested that gamma globulin made from plasma containing antibody to HAA may effectively reduce the risk of post-transfusion hepatitis.[31] Thus far only small scale studies have been recorded, yet the data is encouraging. In contrast, gamma globulin lacking antibody to HAA seems ineffective. Gocke[39] administered plasma containing antibody to Australia antigen to a small group of patients with fulminant hepatitis and reported subsequent amelioration of disease. A controlled prospective study of the potential therapeutic

value of HAA in the treatment of fulminant hepatitis is under way. A patient so treated by our group did not survive.

An experimental hepatitis vaccine was recently prepared by Krugman.[31] The serum, containing HAA, was heat-inactivated and was administered to a small group of children. When challenged with hepatitis inoculations the children who received the heat-inactivated vaccine were apparently immune, whereas hepatitis developed in children not so protected. These studies suggest that a hepatitis vaccine could be feasible. However, it is unlikely that a heat-inactivated vaccine prepared from human serum would lend itself to the extensive safety precautions required for large scale vaccine production. This important work, however, did demonstrate that inactivated HAA may confer protection. It is hoped that this pioneer work will lead to the development of vaccines produced from HAA cultivated in tissue culture and subsequently either attenuated to produce a live attenuated vaccine or inactivated by other methods of inactivation.

Chronic Active Liver Disease

At the time that the presence and persistence of HAA in the sera of some patients with chronic liver disease was demonstrated,[17,18] it was postulated that HAA may be acting as a slow or latent virus. Subsequent studies have confirmed and extended these findings. HAA has been detected in between 10 and 50 percent of patients with chronic active liver disease. During the course of this illness the antigen may come and go, perhaps reflecting variable concentrations of antigen or a varying sensitivity of our HAA assays. HAA may be present even though the liver is cirrhotic.[18] In some instances circulating antigen-antibody complexes have been demonstrated[40] and it has been suggested that these complexes may be important in the progression of this disease. Such complexes may be demonstrated by the detection of anticomplementary (AC) HAA complement fixation assays. Alternatively, antigen and antibody may be demonstrated to coexist in the same serum by application of either the radioimmunoassay or the hemagglutination inhibition assay. Each of these approaches has successfully demonstrated the presence of HAA complexes in some patients with chronic active liver disease.[41] Recent studies by our group have demonstrated that HAA or antigen-antibody complexes may be detected in more than 50 percent of patients with chronic active liver disease.[30] Patients found to have anticomplementary assays tend to have a poorer prognosis than do those who do not. Moreover, patients with circulating immune complexes or anticomplementary assays show the most dramatic response to treatment with prednisone. Unfortunately a large series in which some patients with chronic HAA antigenemia are treated with prednisone and others with placebo has not yet been reported. Our series is not large enough to yield data of statistical significance and hence the question of whether chronic antigenemia lends itself to treatment with prednisone remains unanswered.

Postnecrotic Cirrhosis

Acute hepatitis sometimes progresses to chronic active hepatitis and subsequently to posthepatitic or postnecrotic cirrhosis.[42] In each of these entities, HAA which first developed during acute hepatitis may persist. Thus the presence of HAA among patients with postnecrotic cirrhosis is now well documented.[18] The pathogenic implications of this finding and the associated therapeutic possibilities remain unexplored. The role of HAA in the progression through this spectrum of liver disease is undetermined.

"Persistent Hepatitis," "Unresolved Hepatitis" and "Hippy Hepatitis"

The sequelae of acute hepatitis are numerous. One of these is a benign lesion characterized by a heavy inflammatory infiltrate in portal tracts but not associated with hepatocellular necrosis or lobular destruction. This pathologic lesion has been designated "persistent hepatitis."[43] The same lesion may be found as a result of a number of causes, only one of which is acute hepatitis. Patients with this lesion usually are relatively asymptomatic but may have persistent elevations in transaminase values, and a significant number of such patients may have chronic HAA antigenemia. The natural history of this illness is usually a spontaneous resolution after weeks, months or years. It is not thought to progress to cirrhosis.[44] In contrast, "unresolved hepatitis" is characterized by inflammatory infiltration and variable degrees of hepatocellular necrosis and may be associated with clinical symptoms. It is frequently associated with chronic Australia an-

tigenemia. The natural course of this lesion is not well delineated. Finally, the term "hippy hepatitis"[45] has been applied to chronic liver disease initially thought to be related to the administration of intravenous narcotics. Some cases of this chronic form of liver disease have been found to be associated with Australia antigenemia. Indeed, antigen titers have been found to be unusually high, perhaps because of frequent and heavy exposure.

Neonatal Hepatitis

The role of HAA in maternal and neonatal hepatitis has been extensively investigated. Keyes[25,26] and other members of our group evaluated sera from mothers and infants participating in a collaborative perinatal study encompassing 60,000 pregnancies. Populations studied included mothers with hepatitis during pregnancy, mothers delivering stillborn infants and mothers having repeated abortions. Also studied was cord blood from mothers with hepatitis during pregnancy and from newborns with hyperbilirubinemia, Down's syndrome or elevated immunoglobulin M levels. Of 22 mothers with hepatitis during pregnancy, two were positive for HAA (9.1 percent). HAA may have been acquired by the fetus during intrauterine gestation, since the cord blood from one of the two mothers was also positive. This was the first demonstration of HAA in cord blood. This finding supports the possibility that HAA may be transmitted to the fetus via the placental circulation. In contrast, other investigators had previously suggested that HAA may also be contracted by the fetus from swallowing amniotic fluid *in utero*. HAA was found in one of 30 (3.3 percent) mothers who had repeated stillbirths, in one of 27 (3.7 percent) with repeated abortions, and also in the cord blood of two of 123 mothers (1.6 percent) with elevated IgM levels.

Schweitzer[23] reported the occurrence of HAA in some infants whose mothers had HAA-positive hepatitis. Keyes[26] evaluated 414 pairs of maternal and cord blood specimens from a county hospital population, using the HAA complement fixation and immunodiffusion techniques. Four maternal blood specimens were found to be positive (1 percent). One infant whose mother had HAA at delivery became positive at one month of age. This infant's circulating HAA has persisted throughout the early months of life. Currently the significance of chronic HAA antigenemia in infants is uncertain.

Primary Biliary Cirrhosis and Primary Liver Cell Carcinoma

Two lines of evidence have implicated HAA in the pathogenesis of primary biliary cirrhosis. Electronmicroscopic studies originally revealed antigen-like particles in the sera of a few patients with the disease. Subsequently, highly sensitive assays also detected the antigen in occasional patients with this illness. Recently, a prospective double-blind controlled trial of treatment among patients with chronic active hepatitis yielded other important data which may cast light on the pathogenesis of some cases of primary biliary cirrhosis.[42] Sixty-five patients with chronic active hepatitis were followed prospectively. All had presented with typical clinical, biochemical and histologic features of chronic active hepatitis. Serial biopsy studies were done, and in seven of the patients features characteristic of primary biliary cirrhosis subsequently developed. Of these seven, three were found to harbor HAA. Hence it is suggested that a few patients with chronic active hepatitis may progress to primary biliary cirrhosis, and that HAA, acting as a "slow" virus, may persist in such instances. Thus far most patients having primary biliary cirrhosis do not appear to be HAA-positive, nor do they necessarily pass through a chronic active hepatitis stage. Another unusual outcome of HAA-positive liver disease is the development of primary liver cell carcinoma or hepatoma. Denison recently demonstrated the persistence of HAA in some patients with familial primary liver cell carcinoma.[27] Sherlock[46] had previously observed HAA to be present in some patients with hepatoma.

Polyarteritis, Glomerulonephritis and Arthritis

It has recently been demonstrated that HAA may be detected in some illnesses not ostensibly related to liver disease. Gocke et al[28] evaluated 11 patients with polyarteritis manifested by arthralgia, urticaria, fever, hypertension, hematuria, azotemia and eosinophilia. Four of these 11 patients had circulating serum HAA associated with mild hepatitis. Circulating antigen-antibody

complexes were demonstrated in three of the four patients. Further studies revealed the presence of IgM, HAA and the C^3 component of complement in the walls of a skeletal muscle artery. Evaluation of these patients revealed that most had previously experienced an episode of HAA-positive hepatitis. In another instance, antigen-antibody complexes were demonstrated to be deposited within the glomeruli of the kidneys of a patient with HAA-positive chronic hepatitis and glomerulonephritis.[47] In the latter instance it was postulated that HAA or antigen-antibody complexes may be important in the pathogenesis of the renal lesion. Arthritis simulating rheumatoid arthritis, but lacking rheumatoid factor, may accompany acute or chronic hepatitis. Alpert evaluated nine cases of hepatitis associated with arthritis.[48] Four of the patients had urticaria and four had skin rashes. All patients had HAA in their serum. Serum complement levels or individual complement components were low. Alpert suggested that this may reflect the presence of immune complex disease. Thus emerging evidence suggests that HAA, or antigen-antibody complexes related to HAA, may be important in the pathogenesis of diseases involving organ systems other than the liver.

The Future

As described above, initial data suggests that basic research leading to the cultivation of HAA and the inactivation of HAA may eventually yield an effective and safe hepatitis vaccine. Extensive efforts will be required to cultivate, characterize, attenuate or inactivate the hepatitis virus before a hepatitis vaccine is a reality. Initial data also suggests that HAA detection may have therapeutic and prognostic significance. The detection of HAA circulating immune complexes among patients with chronic active liver disease seems to be an indicator of the need for treatment with steroids.

The significance of HAA in the serum of patients with chronic active liver disease in the absence of immune complexes has yet to be evaluated. Recent data suggests that there are at least four subtypes of HAA. The possible pathogenetic and prognostic significance of HAA subtypes will require extensive research. Early data supports the value of antibody to HAA in the prophylaxis of long incubation period hepatitis, and other data suggests that HAA antibody may have an important therapeutic role in the treatment of fulminant hepatitis. These data will require confirmation and extension.

A Unifying Concept

HAA has now been detected in a variety of illnesses. Firm data establishing the role of HAA in the majority of these illnesses is not available. Circumstantial evidence would suggest that the sequelae of HAA-positive, acute hepatitis include a spectrum of liver disease. Thus the majority of cases resolve without after-effects. A few patients, however, may develop HAA-positive persistent hepatitis, unresolved hepatitis, fulminant, fatal hepatitis, or chronic active hepatitis. Of those in whom chronic active hepatitis develops some may progress to HAA-positive postnecrotic cirrhosis, and hepatoma may develop in a few. Other patients may progress through a chronic active phase into a phase characteristic of primary biliary cirrhosis. Occasional patients with circulating HAA may develop immune complexes which deposit outside of the liver. In the blood vessels polyarteritis may develop and in the kidney glomerulonephritis may be seen. This concept is suggested only as a postulate, for firm data supporting these pathogenetic routes is lacking. Blumberg's initial discovery of HAA has truly led to a revolution in hepatology. Newer concepts of the pathogenesis of liver disease and newer approaches to the treatment of liver disease have become an important part of this revolution.

REFERENCES

1. Allison AC, Blumberg BS: An isoprecipitation distinguishing human serum-protein types. Lancet 1:634, 1961
2. Blumberg BS, Alter HJ, Visnich S: A "new" antigen in leukemia sera. JAMA 191:541, 1965
3. Blumberg BS, Gerstley BJS, Hungerford DA: A serum antigen (Australia antigen) in Down's syndrome, leukemia and hepatitis. Ann Intern Med 66:924, 1967
4. London WT, Sutnick AI, Blumberg BS: Australia antigen and acute viral hepatitis. Ann Intern Med 70:55, 1969
5. Sutnick AI, London WT, Gerstley BJS: Anicteric hepatitis associated with Australia antigen—Occurrence in patients with Down's syndrome. JAMA 205:670, 1968
6. Okochi K, Murakami S: Observations on Australia antigen in Japanese. Vox Sang 15:374, 1968
7. Blumberg BS: An inherited serum isoantigen in leukemia and Down's syndrome. J Clin Invest 45:988, 1966
8. Blumberg BS, Melartin L, Guinto RA: Family studies of a human serum isoantigen system (Australia antigen). Am J Hum Genet 18:594, 1966
9. Blumberg BS, Friedlaender JS, Woodside A: Hepatitis and Australia antigen—Autosomal recessive inheritance of susceptibility to infection in humans. Proc Nat Acad Sci USA 62:1108, 1969
10. Sutnick AI, London WT, Blumberg BS: Australia antigen and the quest for a hepatitis virus. Am J Dig Dis 14:189, 1969
11. Shulman NR, Barker LF: Virus-like antigen, antibody, and antigen-antibody complexes in hepatitis measured by complement fixation. Science 165:304, 1969

12. Purcell RH, Holland PV, Walsh JH, et al: A complement fixation test for measuring Australia antigen and antibody. J Infec Dis 120:383, 1969

13. Bayer ME, Blumberg BS, Werner B: Particles associated with Australia antigen in the sera of patients with leukemia, Down's syndrome and hepatitis. Nature (London) 218:1057, 1968

14. Millman I, Zavatone V, Gerstley BJS, et al: Australia antigen detected in the nuclei of liver cells of patients with viral hepatitis by the fluorescent antibody technique. Nature (London) 222:181, 1969

15. Prince AM: An antigen detected in the blood during the incubation period of serum hepatitis. Proc Natl Acad Sci USA 60:814, 1968

16. Prince AM: Relation of Australia and SH antigens. Lancet 2: 462, 1968

17. Wright R, McCollum RW, Klatskin G: Australia antigen in acute and chronic liver disease. Lancet 2·117, 1969

18. Gitnick GL, Gleich GJ, Schoenfield LJ, et al: Australia antigen in chronic active liver disease with cirrhosis. Lancet 2:285, 1969

19. London WT, DiFiglia M, Sutnick AI, et al: An epidemic of hepatitis in a chronic hemodialysis unit—Australia antigen and differences in host response. N Engl J Med 281:571, 1969

20. Raunia VK, London WT, Sutnick AI, et al: Specifications of human antibodies to Australia antigen. Proc Soc Exp Biol Med 134: 548, 1970

21. Kim CY, Tillis JG: Immunologic and electrophoretic heterogeneity of hepatitis associated antigen. J Infect Dis 123:618, 1971

22. Le Bouvier GL: Heterogeneity of Australia antigen. J Infect Dis 123:671, 1971

23. Schweitzer IL, Spears RL: Hepatitis associated antigen (Australia antigen) in mothers and infant. N Engl J Med 283:570, 1970

24. Newan SJ, Madden DL, Gitnick GL, et al: A serological survey for Australia antigen and antibody. Am J Dis Child 122:129, 1971

25. Keyes TF, Sever JL, Gitnick GL, et al: Hepatitis associated antigen in selected maternal and newborn populations. Pediatrics (In press)

26. Keyes TF, Hobel CJ, Ritman S, et al: Maternal and neonatal Australia antigen. Calif Med (In press)

27. Denison EK, Peters RL, Reynolds TB: Familial hepatoma with hepatitis-associated antigen. Ann Intern Med 74:391, 1971

28. Gocke DJ, Hsu K, Morgan C: Association between polyarteritis and Australia antigen. Lancet 2:1149, 1970

29. Prince AM, Trepo C: Role of immune complexes involving SH antigen in pathogenesis of chronic active hepatitis and polyarteritis nodosa. Lancet 1:1309, 1971

30. Gitnick GL, Soloway RS, Summerskill WHJ, et al: Significance of Australia antigen and anti-complementary assays in chronic active liver disease (In submission)

31. Krugman S, Giles JP, Hammond J: Viral hepatitis Type B (MS-2 strain)—Studies on active immunization. JAMA 217:41, 1971

32. Sturgeon P, Kwak KS, Gitnick GL: Australia antigen detection by a rapid automated complement fixation method. Vox Sang 20:533, 1971

33. Vyas GN, Shulman NR: Hemagglutination assay for antigen and antibody associated with viral hepatitis. Science 170:332, 1970

34. Walsh JH, Yalow R, Berson SA: Detection of Australia antigen and antibody by means of radioimmunoassay techniques. J Infect Dis 121:550, 1970

35. Giles JP, McCollum RW, Berndtson LWJ, et al: Viral hepatitis; relation of Australia/SH antigen to the Willobrook MS-2 strain. N Engl J Med 281:119, 1969

36. Krugman S, Giles JP, Hammond J: Infectious hepatitis: Evidence for two distinctive clinical, epidemiological and immunological types of infection. JAMA 200:365, 1967

37. Krugman S, Giles JP: Viral hepatitis—New light on an old disease. JAMA 212:1019, 1970

38. Krugman S: Viral hepatitis: New clinical, epidemiological and immunological concepts. Calif Med 113:57-59, Jul 1970

39. Gocke DJ: Fulminant hepatitis treated with serum containing antibody to Australia antigen. N Engl J Med 284:919, 1971

40. Millman I, London WT, Sutnick AI, et al: Australia antigen-antibody complexes. Nature 226:83, 1970

41. Brzosko WJ: Australia antigen immune complexes in patients with different forms of hepatitis. J Infect Dis 123:251, 1971

42. Soloway RD, Geall MG, Gitnick GL, et al: Clinical, biochemical and histologic remission of severe chronic active liver disease: A controlled study of treatments and early prognosis. (In submission)

43. de Groote J, Desmet VJ, Gedigk P, et al: A classification of chronic hepatitis. Lancet 2:629, 1968

44. Becker MD, Scheuer PJ, Baptista A, et al: Prognosis of chronic persistent hepatitis. Lancet I:53, 1970

45. Barret P, Boyle DJ, Samloff M: Hippie hepatitis. Gastroenterology 54:1219, 1968

46. Sherlock S, Fox RA, Niazi SP, et al: Chronic liver disease with primary liver-cell cancer with hepatitis associated (Australia) antigen in serum. Lancet I:1243, 1970

47. Combes B, Stastny P, Shorey J, et al: Glomerulonephritis with deposition of Australia antigen-antibody complexes in glomerular basement membrane. Lancet 2:234, 1971

48. Alpert E, Isselbacher KJ, Schur PH, et al: Pathogenesis of arthritis associated with viral hepatitis. N Engl J Med 285:185, 1971

RECURRING PNEUMONIA IN INFANTS?—THINK OF OBSTRUCTION

What should you be on the look-out for when you see persistent or recurring pneumonias in the infant or young child?

In the broadest terms it would be bronchial obstruction. The natural tendency is to think of foreign body obstruction first which actually, despite its importance, is not very common. You think of compression of the bronchus due to lymphadenopathy, not as common now as formerly when there was a childhood tuberculosis. The most common cause is none of these dramatic things, but just the simple retained secretions following acute lower respiratory infections. Part of the lung becomes poorly aerated, and secretions are so tenacious they are not coughed up; spontaneous mechanisms just don't seem to take care of the situation in many cases. This is recognized, of course, only when bronchoscopy is done. I think we do have to think of the obvious mechanical causes of obstruction, but not disregard the simpler and more frequent matter of retained secretions following acute respiratory infection.

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